

**Study Title:** Pain Coping Skills Training for African Americans With Osteoarthritis

**NCT number:** NCT02560922

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## PCORI RESEARCH PLAN TEMPLATE

### RESEARCH STRATEGY

#### A. BACKGROUND

**A.1.0 Osteoarthritis (OA) is a Highly Prevalent and Disabling Health Problem.** OA is one of the most common chronic diseases in the U.S.; about 27 million adults have symptomatic OA <sup>1,2</sup>. Because of the forecasted growth in the U.S. older adult population, the prevalence of OA is expected to double over the next several decades <sup>3</sup>. OA is also the most frequently reported cause of disability in the U.S.<sup>4</sup>, commonly affecting walking, stair-climbing, and other daily tasks. Among older adults, the risk of disability attributable to knee OA is as great as that due to cardiovascular disease and greater than any other medical condition <sup>5</sup>. In addition to pain and disability, OA has detrimental effects on other important patient-centered outcomes such as depression, anxiety, sleep, fatigue, physical activity, weight gain, and quality of life <sup>6-9</sup>. **OA is a large and rapidly increasing public health problem that takes a substantial personal toll on many adults.**

**A.2.0 African Americans Bear a Disproportionate Burden of OA Across Many Patient-Centered Outcomes.** A number of studies show that African Americans not only experience a greater prevalence of OA than Caucasians, but also more severe pain, functional limitations, and other adverse outcomes <sup>10-14</sup>. Among adults in the National Health Interview Survey with arthritis (most commonly OA), African Americans were more likely than Caucasians to report having activity limitations attributable to arthritis (44% vs. 34%) and severe joint pain (34% vs. 23%);<sup>15</sup> they were also 1.5 times as likely to be limited in their social participation<sup>16</sup>. In a community-based study in Johnston County, North Carolina, African Americans with knee OA had significantly worse scores than Caucasians on the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC), a measure of pain, stiffness and function (32.8 vs. 24.3, respectively,  $p < 0.001$ ) <sup>17</sup>. Among about 900 Veterans with knee or hip OA, African Americans had significantly worse WOMAC scores than Caucasians (61 vs. 55,  $p < 0.001$ ) <sup>18</sup>. In our clinical trial of Veterans with knee or hip OA <sup>19</sup>, African Americans also had worse WOMAC scores (52.3 vs. 44.5,  $p < 0.001$ ) and more arthritis-related activity limitation (6.1 vs. 4.8 on scale of 0-10,  $p < 0.001$ ) compared to Caucasians. In both the Johnston County and Veteran samples, racial disparities in WOMAC scores reflect clinically relevant differences <sup>20</sup>. These studies signal an obvious need to address the disproportionate burden of OA among African Americans. **In fact, the Institute of Medicine has identified interventions to reduce disparities in OA and other musculoskeletal diseases among its top 25 (highest tier) priority topics for comparative effectiveness research** <sup>21</sup>.

#### B. SIGNIFICANCE

**B.1.0 Overview of the Project's Potential to Impact Health Care and Outcomes.** This project has great potential to impact health care and outcomes by improving pain and other patient-centered outcomes for the large number of African American patients who have OA. Despite many years of research highlighting the disproportionate burden of pain-related conditions (including OA) among African Americans, very little has been done to address these disparities <sup>22</sup>. **A recent review noted that one key barrier to moving this research forward has been limited engagement by minority patient groups; as a result, pain management theories, concepts, and interventions have gone largely un-tested in minority patient groups including African Americans (RQ-1)** <sup>23</sup>. Pain Coping Skills Training (CST), a cognitive-behavioral intervention with shown efficacy to improve OA-related pain and other patient-centered outcomes, has strong potential to benefit African Americans with OA (see Section B.2.0). However, stakeholder input and a stronger evidence base for the effectiveness of pain CST among African Americans is needed, particularly in the context of real-world settings (RQ-1). Pain management interventions like CST are highly under-utilized <sup>24,25</sup>, and primary care providers typically do not have the time or training to work with patients on key evidence-based pain coping skills. Therefore, incorporation of pain CST programs into health care and other settings that reach large numbers of African Americans with OA would have a substantial impact on care, satisfaction, and other patient-centered outcomes. Accordingly, this project will develop and test a pain CST program that

could be readily implemented in diverse clinical and other settings. In the following sections we describe research that further supports the potential of this project to improve health care and outcomes.

### **B.2.0 Pain Coping Skills Training is a Highly Promising Strategy to Address Racial Disparities in OA**

**B.2.1 There are Racial Differences in Pain Coping and Perceived Pain Control.** Studies show that when compared with Caucasians, African Americans with OA (and other chronic pain conditions) report greater levels of pain catastrophizing (i.e., the tendency to focus on and magnify pain sensations and to feel helpless in the face of pain<sup>26-29</sup>), lower perceived ability to cope with and control pain<sup>30,31</sup>, and greater maladaptive coping strategies (i.e., emotion-focused or external coping strategies)<sup>30,32-34</sup>. This is very important because these coping-related characteristics have been associated with worse pain, function, and depressive symptoms<sup>35-38</sup>. **Of particular relevance, these coping patterns can be modified through pain CST<sup>39-43</sup>.**

**B.2.2 Coping and Psychological Variables are Contributors to Racial Disparities in Pain and Function.** We have conducted analyses of three separate cohorts, showing that **coping patterns and related psychological variables are important contributors to racial differences in pain and function.** Most recently, we assessed the role of pain catastrophizing as a potential mediator of racial differences in pain among 300 patients with hip and knee OA enrolled in a clinical trial<sup>19</sup>. WOMAC pain subscale scores were worse among African Americans than Caucasians in this sample (11.0 vs. 9.4 on a scale of 0-20). In a simple regression model of WOMAC pain scores, the estimate for race was -1.6 (CI= -2.5, -0.8,  $p < 0.001$ ). When scores on the Pain Catastrophizing Scale were added to this model (with no other covariates), the regression coefficient for race became non-significant (-0.7, CI= -1.5, 0.1,  $p > 0.05$ ); greater Pain Catastrophizing scores were associated with worse WOMAC pain scores in this same model (regression coefficient = 2.1, CI= 1.7, 2.4),  $p < 0.001$ . **These results indicate that Pain Catastrophizing – a primary target of the proposed intervention - mediated the association of race with WOMAC pain scores in this patient group, with no other covariates included in the model.**

Second, we previously found that in a separate cohort of African American (N=221) and Caucasian (N=270) Veterans with knee and / or hip OA, racial differences in baseline pain and function scores were no longer significant when controlling for participant characteristics including emotion-focused coping (Table 1)<sup>34</sup>. This is relevant to the proposed study because emotion-focused coping has been associated with worse pain-related outcomes and is addressed by the pain CST program. Third, we examined associations of race and other variables with WOMAC scores (pain and physical function) among n=1,368 participants with knee OA (32% African American) in the community-based Johnston County Osteoarthritis Project<sup>17</sup>. Radiographic severity and demographic factors did not explain racial differences in pain and function. However, depressive symptoms were an important mediator of this association. These results provide further support for the potential impact of CST among African Americans with OA, since studies show that CST positively influences psychological health, including depression<sup>39,44,45</sup>.

### **B.2.3 Preliminary Data Indicate Pain CST Programs May Particularly Benefit African Americans with OA.**

**Although prior clinical trials support the efficacy of CST programs for improving pain and other outcomes among patients with OA<sup>39,41,44,46-50</sup>, these studies have involved primarily non-minority samples and have not obtained patient perspectives on cultural appropriateness. Importantly, results of our recent pilot study (Drs. Allen, Keefe, and Campbell) indicate CST may be particularly beneficial for African Americans with OA and may reduce disparities in pain, coping strategies and other outcomes.** The first step in this pilot work involved focus groups of African American Veterans with OA, where

**Table 1. Results of Multivariable Linear Regression Model of AIMS2 Pain and Function Scores**

	<b>AIMS2 Pain *</b>	<b>AIMS2 Function*</b>
	B (p-value)	B (p-value)
African American	0.03 (0.874)	0.09 (0.419)
Emotion-Focused Coping <sup>†</sup>	0.15 (<0.001)	0.18 (<0.001)
Arthritis Self-Efficacy	-0.30 (<0.001)	-0.17 (<0.001)
AIMS2 Affect Subscale	0.29 (0.028)	0.23 (<0.001)
Age	-0.01 (0.080)	--
Perceived Inadequate Income	0.19 (0.342)	0.15 (0.245)
Fair or Poor Health	0.64 (<0.001)	0.91 (<0.001)
* AIMS-2 = Arthritis Impact Measurement Scales-2; higher scores = worse pain and function. † Higher scores = more emotion-focused coping.		

we obtained input on a pain CST program based on prior work by Dr. Keefe and colleagues; this included exploration of issues related to cultural relevance (e.g., concordance of intervention content with values, norms, and beliefs). Feedback from the focus groups was incorporated into the pain CST program. Next we evaluated the telephone-based CST intervention among  $n=30$  patients at the Durham VA Medical Center (VAMC) with clinically documented OA (mean age = 58 years; 9 females; 14 Caucasians, 13 African Americans, 3 other racial / ethnic minorities). Outcomes were assessed at baseline and 12-week follow-up and included AIMS-2 subscales (pain, affect, mood, and physical function) and the Coping Skills Questionnaire <sup>51</sup>.

As shown in Appendix Table 1, African American participants improved in all Arthritis Impact Measurement Scales-2 (AIMS-2) subscales, with statistically significant changes from baseline ( $p<0.05$ ) for the Total, Pain, Walking and Bending, and Mood subscales. **Also importantly, African Americans exhibited greater improvements than Caucasians in all AIMS-2 subscales.** In addition, African Americans (but not Caucasians) had a significant ( $p<0.05$ ) decrease (improvement) in pain catastrophizing scores. This result is particularly relevant, given the strong and consistent association between high pain catastrophizing and greater pain severity <sup>35-37</sup>. The following quote from an African American patient in this pilot study illustrates the value of the CST program from the patient perspective, *“Before the program I really didn’t have the right tools in order to get rid of the pain. Now...I actually do have tools in order to be able to make the pain decrease ...”* **In summary, results of this pilot study suggest that the proposed CST program, with cultural tailoring, may be particularly beneficial for African Americans OA and may be a key strategy for reducing racial disparities.** However, work is still needed to: 1.) Engage the full range of Stakeholders in the process of evaluating this CST program and its dissemination potential, with particular attention to cultural relevance. 2.) Conduct a larger clinical trial of pain CST among African Americans with OA to examine effectiveness in real-world settings. 3.) Create practical tools (“deliverables”) to facilitate dissemination and implementation of this program in community and clinical settings that reach African Americans with OA.

### **B.3.0 Overview of the Patient-Centeredness of the Study**

The proposed project is highly patient-centered because OA is a leading cause of pain and disability <sup>4,52</sup>, outcomes that are consistently endorsed by patients as being of high importance (**RQ-6**) <sup>53-55</sup>. OA-related pain also has a detrimental impact on other key patient-centered outcomes such as depression, anxiety, employment, relationships, sleep, fatigue, employment, and quality of life <sup>6-9</sup>. In addition, arthritis is a key barrier to engaging in other healthy behaviors, such as physical activity, and it is strongly associated with obesity <sup>56-58</sup>. Therefore interventions that help patients manage OA-related pain also have tremendous potential for affecting other health outcomes of importance to patients <sup>59</sup>. This is particularly important for African Americans with OA, since they bear a disproportionately high burden of symptoms.

**This project addresses the key PCORI question, “What can I do to improve the outcomes that are most important to me?”** Specifically, information generated from this project will enable African Americans with OA to know whether participating in a pain CST program will improve key patient-centered outcomes (**RQ-3**). Participation in these types of programs requires a time investment by patients, and sometimes friends or family members who take over responsibilities to enable patients to participate. Therefore it is important to provide solid information on likely benefits, so patients can choose whether to invest their time in a pain CST program. We have applied patient-centered principles to all aspects and stages of the study conduct, summarized in Table 2 below, with details on these approaches provided the remainder of the proposal.

### **B.4.0 Other Preliminary Studies**

In addition to our work described in Section B.2, we have completed other studies that demonstrate our commitment to this research area and our experience that will allow successful completion of the project:

**B.4.1 Pain CST Studies by Study Team Members / Culturally Enhanced Protocols.** Drs. Keefe, Somers, and Campbell have conducted extensive work on pain CST interventions. Dr. Keefe is the developer of the CST intervention upon which the proposed intervention is based. He has led an active program of research involving trials of this intervention and is an international expert in the area of pain coping and outcomes <sup>39,41,44,46,48,49,59,60</sup>. Dr. Campbell has worked closely with Dr. Keefe in studies of OA patients and has adapted the CST intervention for African Americans with cancer <sup>61</sup>. Dr. Campbell received a Minority Supplement to enhance the cultural sensitivity of basic elements of the CST protocol for this patient group and has been the

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): ALLEN, KELLI DOMINICK

**Table 2. Patient-Centered Approaches to Study Conduct**

Study Aspect	Patient-Centered Approach(es)
Participant Recruitment	<ul style="list-style-type: none"> <li>Recruitment materials reviewed by Patient Stakeholders for understandability and cultural relevance</li> <li>Enhanced consent process with increased attention to patient rights in research</li> <li>All initial study activities (consent, assessments) done at one appointment to minimize participant burden</li> </ul>
Pain CST Intervention	<ul style="list-style-type: none"> <li>Telephone-based delivery to facilitate access and flexible scheduling for patients</li> <li>Availability of evening and weekend sessions</li> <li>Incorporation of enhancements to address issues of cultural relevance</li> <li>Comprehensive approach that integrates comorbid health conditions and other behaviors important for OA management</li> </ul>
Measures	<ul style="list-style-type: none"> <li>Primary outcome (pain) is the central symptom for patients with OA</li> <li>Inclusion of a global quality of life measure, as recommended by Patient Stakeholders, to capture the impact of OA on many aspects of patients' lives</li> </ul>
Dissemination Potential	<ul style="list-style-type: none"> <li>Outreach to community-based organizations that serve many older African Americans; taking the intervention results and deliverables to "familiar ground."</li> <li>Use of patient testimonials to help patients see the impact of pain CST on "people like me"</li> </ul>

principal investigator of 2 studies (DOD and NIH-funded) evaluating the efficacy of culturally enhanced protocols in African American men with prostate cancer and their intimate partners. Dr. Campbell's adaptations to CST protocols were designed to increase the cultural congruence of CST, such that intervention elements were not in conflict with norms common to many African American communities. Norms identified in Dr. Campbell's work included the stigma attached to seeking psychological services and the importance of productivity and not appearing lazy in the eyes of family, friends, and community. To address the issue of stigma, CST was presented as an educational intervention rather than a form of treatment or therapy. Concerns related to productivity were addressed in two ways. First, communication strategies were taught in the intervention to provide participants with strategies for explaining CST to family and friends and requesting any support needed to fully participate in CST (e.g., a break from some household duties, time off from church committee work). Second, strategies involving rest or relaxation were taught with an emphasis on how rest and

relaxation can ultimately improve stamina or performance in the long-term. These adaptations will be integrated into the proposed pain CST intervention for African Americans with OA and reviewed by the Stakeholder Panel.

**B.4.2 Clinical Trials of Behavioral Interventions for Patients with OA.** In addition to a completed clinical trial of telephone-based OA self-management<sup>62,63</sup>, Dr. Allen and colleagues have recently conducted two clinical trials (one at Duke, one at the Durham VAMC) of Patient and Provider Interventions for Managing OA in Primary Care,<sup>19</sup> a clinical trial comparing group vs. individual approaches to delivering physical therapy for knee OA in the VA healthcare system,<sup>64</sup> and a clinical trial of decision aids for patients with hip and knee osteoarthritis<sup>65</sup>. Dr. Allen is also currently leading a clinical trial of physical therapy vs. internet-based exercise training for patients with knee OA, funded by the Patient-Centered Outcomes Research Institute. These studies demonstrate our team's experience in all aspects of conducting clinical trials among patients with OA, including recruitment, retention, intervention delivery and outcome assessment. Although these prior trials have not exclusively enrolled African American patients, they have involved a substantial number of participants from this minority group. For example, in our trials of Patient and Provider Interventions for Managing OA in Primary Care, about 40% of 537 participants (N=212) from the Duke-based study and 50% of the 300 patients in the VA-based study are African American. **This demonstrates our experience with reaching out to African Americans with OA in the context of clinical trial participation.** We also note that in both of these trials, rates of enrollment were similar to or better among African American patients compared to Caucasian patients. In the Duke study, 53.6% of invited African American patients and 56.5% of invited Caucasian patients agreed to participate. In the VA study, 56.4% of invited African American patients agreed to participate, compared to 40% of invited Caucasians patients.



## C. STUDY DESIGN & APPROACH

### C.1.0 Overview and Adherence to PCORI Methodology Standards

All study methods have been developed with reference to the PCORI Methodology Standards. Throughout the remainder of the proposal, we reference sections of the Methodology Standards (in bold print, using PCORI Appendix A labels) that are addressed by elements of the research plan. Sections C-G serve as a protocol for this planned effectiveness clinical trial (**RQ-2**).

### C.2.0 Incorporation of Stakeholder Perspectives into CST Program (Specific Aim 1)

The first Specific Aim of this project is to: "Engage African American patients with OA, their support partners, health care providers, clinic administrators, and public health representatives in a process of evaluating and refining a pain CST program for culturally appropriate content and dissemination potential." There is a growing body of literature supporting the efficacy of health interventions that have been tailored to specific racial, ethnic, and cultural groups<sup>61,66-69</sup>. A recent review indicates that mental health interventions are more effective when adapted to meet the needs and expectations of minority populations<sup>70</sup>. There are also specific reasons we believe it is particularly important to consider issues of cultural relevance of a pain CST intervention among African Americans with OA. **First**, most studies of pain CST among patients with OA have involved predominantly Caucasian samples. Therefore the extent to which the CST intervention matches the cultural characteristics, values, and pain experiences of African Americans is not well understood. As described above, Dr. Campbell's work has identified issues related to the stigma of psychological services and the importance of productivity among African American men with prostate cancer; these areas, as well as others identified by our Patient Stakeholders and their supportive partners, will be further explored and incorporated into the intervention. **Second**, African Americans often experience a greater number and different types of stressful events (i.e., socioeconomic, environmental, occupational, racism-related) than Caucasians, and these stressors can be important contributors to the pain experience<sup>71</sup>. One focus of the CST intervention is applying pain coping skills in the context of stressful events. Because of racial differences in the types and volume of stressors patients may experience, African Americans may experience barriers to incorporating pain coping skills in stressful situations. We will explore the areas of compound stressors and capacity to deal with race-related stressors with our Patient Stakeholders. **Third**, one core cultural value of many African Americans is religion or spiritualism, and African Americans tend to employ more religious coping strategies than Caucasians<sup>71,72</sup>. While the coping skills involved in the CST intervention are not implicitly religious, these aspects can be incorporated when religion or spirituality is a core value for participants. For example, prayer can be incorporated into relaxation exercises, and coping self-statements can be based on Scripture or other texts. For some participants, pain may interfere with church attendance and result in the loss of a meaningful activity. Activity pacing may allow for a return to church by staying for shorter periods.

We have already taken initial steps to evaluate issues of cultural relevance of pain CST, including our pilot study among African American Veterans with OA described above. However, there is still a need for broader Patient Stakeholder input, particularly since our pilot study involved primarily male Veterans. As described below (Section G), we have been meeting with Patient Stakeholders during the course of this proposal development; we have presented the CST program (and other aspects of the study) to these stakeholders and have incorporated their input into the proposal. For example, one theme we heard from several patients was the important role of family or friends in the pain and pain management experience. Based on this input, we have added a module to the pain CST program that will teach patients effective skills for communicating with others about their pain and soliciting support (similar to Dr. Campbell's work described above) and have invited supportive others to participate on the Stakeholder Panel. At the beginning of the study period, we will continue to work with Stakeholder Panel members to finalize the pain CST program. (In addition, Section G describes details of our Stakeholder Engagement plan relevant to Specific Aim #1.)

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Following incorporation of Stakeholder Panel input into the pain CST program, we will present this version to a separate group of approximately eight African American patients with OA. We will identify potential stakeholders for this group in several ways, including referrals from providers, advertisements in clinics, and an email to UNC employees. The CST counselor or other qualified study team member will present each session to these patients via telephone, so they can experience the program in the same delivery format that will be used among study participants. Feedback from these patients will then be incorporated into the CST program prior to beginning the clinical trial. Table 3 provides a summary of the ways in which the CST program has been culturally enhanced to date (based on our Veteran pilot study and informed by Dr. Campbell's work), as well as examples of other areas where additional enhancements could be applied, based on our initial work with the Stakeholder Panel and pilot testers.

<b>Table 3. Examples of Cultural Enhancements to Pain CST Program</b>	
<b>Enhancements Based on Previous Work</b>	
<b>Traditional CST Program Approach / Patient Concern</b>	<b>Culturally Enhanced CST Program Approach</b>
Described as "treatment" or "therapy"	Described as an educational intervention to deal with the stigma of psychological services
Some aspects of CST perceived as not promoting productivity	Added a module on communication strategies to help patients talk with family and friends about CST skills and their need for support in managing pain Relaxation skills emphasize their ability to improve long-term productivity
Literacy level too high for some patients	Simplified and lowered the reading level of patient handouts
<b>Examples of Potential Additional Enhancements (Based on Stakeholder Input)</b>	
Pain coping skills difficult to apply in context of compound / extreme life stressors	Provide additional and specific guidance on applying these skills in the types of situations noted by patients
Time constraints for home practice (may be a challenge for women with multiple caregiving roles)	Allocate intervention time to helping patients develop specific plans for integrating their home practice and prioritize home practice assignments once multiple skills have been learned
Concern about whether program conflicts with religious values	Add specific content in intervention scripts and handouts on how coping skills can be aligned with patients' religious beliefs, traditions and values

### **C.3.0 Clinical Trial Design (Specific Aims 2 and 3)**

The clinical trial will address Specific Aims 2 and 3:

**Specific Aim 2:** Examine the effectiveness of an 11-session, culturally enhanced, telephone-based pain CST program among African Americans with hip or knee OA.

**Specific Aim 3:** Examine whether individual patient characteristics (particularly baseline pain catastrophizing score, comorbidity and duration of OA symptoms) are associated with differential improvement in the pain CST program.

Figure 1 shows the design and measurement points for the clinical trial. This will be a randomized controlled trial, with equal allocation of participants to pain CST and Wait List Control (WL) groups. The WL group mirrors a “usual care” condition, since this study involves patients who are under treatment for hip or knee OA at the University of North Carolina (UNC) Health Care System and the Durham VAMC (RQ-5); all participants will continue other usual care for knee OA during the study period. (A description of participants and recruitment methods is provided in Section E, and detail on the enrollment sites is provided in Section F.)

Randomization will be stratified according to enrollment site and gender, to ensure that the groups are balanced in these respects. The two points for follow-up assessments will be at approximately 12 weeks and 36 weeks. The 12-week time point will follow intervention completion. To allow for the brief lag time between the baseline visit and randomization / first intervention call, as well as the potential for missed calls and scheduling conflicts, we will schedule follow up assessments between 14 and 16 weeks after the baseline visit. The 36-week time point, about six months after intervention completion, will allow us to evaluate whether any intervention effects are sustained once CST group participants are no longer in a period of active intervention. Participants in the WL group will be invited to take part in the CST program following all study assessments.

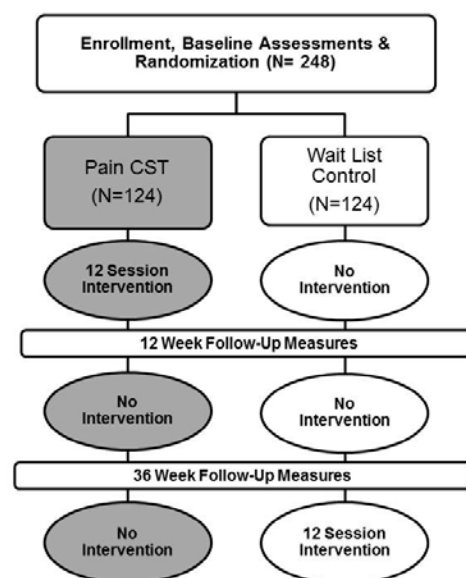
Because chronic pain conditions often impact family members and friends who can help to support coping strategies, we considered studying a partner-based pain CST program<sup>42</sup>. However, we were concerned that this strategy would exclude African American patients who do not have a close supportive partner to participate in the pain CST program with them. This concern was highlighted by work with our patient stakeholders, some of whom are not married and do not have a consistent support partner in the context of managing their pain and its daily impact. Therefore we have adopted what we believe is a patient-centered approach to this issue. Specifically, we will include intervention modules that help patients to engage and communicate with their support partners when available (or to seek additional support for their pain coping, when appropriate). We believe this strategy will provide the advantages of involving support partners while not introducing restrictions that would exclude patients from the study.

#### C.4.0 Overview of the Pain CST Intervention (RQ-5)

Rationale and Theoretical Basis for Pain CST. There are a number of theories that link pain experiences with psychological and behavioral processes, including the gait control theory<sup>73</sup> and its expansion the neuromatrix theory<sup>74</sup>. These theories highlight that pain is a complex experience that influences and can be influenced by brain processes related to sensation, cognition, emotion, and behavior. A core concept of these theories is that noxious pain impulses are influenced by a gating mechanism within the spinal cord. The gate can be opened by physical factors (e.g., injury), psychological factors (e.g. depression), and behavioral factors (focusing on the pain). The gate can also be closed by physical factors (e.g., analgesic use), emotional factors (e.g., positive mood), and behavioral factors (e.g., distraction from the pain). **An important implication is that systematic training in skills for altering thoughts, feelings, and behaviors related to pain can reduce pain and minimize its detrimental impact on psychological and physical functioning<sup>75</sup>.**

General Components of the CST Program. This CST program will be based on a model developed by Dr. Keefe and colleagues. There basic components of the intervention are<sup>75</sup>:

Figure 1. Overview of Trial Design





**1. Education in Rationale for CST.** Patients are provided with a brief rationale for the CST intervention, including components of gate control theory, which helps them to understand how their thoughts, feeling, and behaviors can influence pain and how learning coping skills can enhance their ability to control pain.

**2. Counselor-Guided Training in Coping Skills.** A counselor provides instruction in cognitive and behavioral pain coping strategies and also leads patients in guided behavior rehearsals of these skills. The following are main categories of cognitive and behavioral coping strategies, along with cultural enhancements we anticipate may be important, based on our pilot work:

**Cognitive Restructuring.** Cognitive restructuring is a process by which patients are taught to recognize the relationships between thoughts, feelings and behavior <sup>76</sup>. Patients are taught to identify overly negative, maladaptive thoughts regarding pain and to replace those with alternative, more realistic and helpful coping thoughts that enhance pain coping efforts and pain control. This component of the intervention was adapted from a self-instructional training intervention by Turk et al. <sup>77</sup>. *This skill is one for which cultural tailoring may involve more detailed or systematic incorporation of spiritual or other cultural values into thoughts about pain and pain management.*

**Attention Diversion Methods.** Patients are trained in three attention diversion methods to enhance pain control: relaxation, imagery, and distraction. Relaxation training is based on a protocol described by Surwit et al. <sup>78</sup>, involving concentration of muscle tension and then using this as a cue to relax. Imagery is taught as an adjunct to relaxation <sup>79</sup>. Patients practice using pleasant imagery and changing from one image to another. Distraction techniques help patients focus on physical or auditory stimuli <sup>79</sup>. *This skill is one for which cultural tailoring may involve addressing norms about the acceptability of relaxation.*

**Changing Activity Patterns.** Patients are taught how to change activity patterns to control pain via strategies for activity-rest cycling <sup>80</sup> and pleasant activity scheduling <sup>81</sup>. In activity-rest cycling, patients identify activities in which they may overexert themselves, learn to break up those activities into periods of activity and rest (i.e., 20 minutes of housework followed by 10 minutes of rest), and gradually increase their activity level and decrease resting periods. With respect to pleasant activity scheduling, patients identify activities they enjoy and make weekly plans for engaging in these activities. *This skill is one for which cultural tailoring may involve greater attention to life challenges or demands that present challenges to planning and controlling activity patterns.*

**Communication with Supportive Others about Pain and Coping.** *One enhancement we have made to the CST program, based on Patient Stakeholder input, is the importance of others in dealing with chronic pain.* Therefore we have added a module that provides guidance in speaking and listening strategies and expressive vs. decision-making conversations, all applied to communicating with supportive others about pain.

**3. Home Practice and Maintenance Planning.** Patients are asked to engage in home-based practice of the coping skills to enhance their ability to apply these skills effectively in pain-related situations. The counselor addresses participants' home practice, including successes and barriers, during intervention sessions.

**4. Consideration of Other Lifestyle Factors Important for OA Management.** The CST counselor will work with participants to place pain CST in the broader context of OA management. Physical activity and weight management are particularly important lifestyle strategies for managing OA <sup>85,86</sup>. Although pain CST will be the focus of this intervention, we will also support participants' engagement in these other lifestyle approaches, using low literacy materials and intervention scripts we developed in other studies <sup>19</sup>. These materials take a behavioral, goal-setting approach to weight management and physical activity. Sessions 8 and 9 of the program will address physical activity and weight management, respectively (See Appendix). This order was selected strategically, since each of the pain coping skills will have been introduced by that time point, and the counselor will be able to work with participants to integrate those skills in their efforts to change physical activity and dietary patterns. For example, activity-rest cycling is important for helping patients to improve overall physical activity without pain exacerbation. Cognitive restructuring is also important for helping patients to address unhelpful thoughts that link pain to these other behaviors. For example, some individuals respond to pain with unhealthy eating patterns; uncovering and addressing unhelpful pain-related thoughts is a key to

changing these patterns. The CST counselor may also address participants' comorbid illnesses in the context of engaging in weight management and physical activity, as well as the use of pain coping skills.

### **C.5.0 Schedule and Specific Content of the Pain CST Program**

The CST intervention will involve 11 weekly sessions, conducted via telephone to enhance accessibility and reach. In particular, the telephone-based delivery of this program makes it one that could be delivered to patients across a wide geographic area with small central oversight. Based on our pilot work, we anticipate each of the sessions will take approximately 30-45 minutes, and this was very acceptable to participants. The content of the CST interventions will be based on the Coping Skills Training Manual (Osteoarthritis Version), developed by Dr. Keefe and colleagues, which provides detailed session-by-session information, instructions for counselors, and patient handouts<sup>39,41,44,49</sup>. As part of our VA-based pilot study described above, we adapted the counselor instructions and patient manual (See Appendix) into a lower literacy format. As noted above, we will also utilize low literacy materials from our recent OA studies to incorporate sessions on physical activity and weight management. As described in Specific Aim #1, further adaptations will be made to incorporate other issues of cultural relevance based on Stakeholder input. The patient manual, as well as an audio-recording of relaxation instructions, will be provided to participants. Each session includes: teaching and / or review of specific coping skills, counselor-led practice of coping skills, review of practice and use of skills during the prior week, and developing individual plans and goals for home practice of skills for the next week. Participants are asked to document weekly goals.

### **C.6.0 Training and Supervision of CST Counselor**

We will follow procedures established by Dr. Keefe and colleagues regarding training and supervision of the CST counselor. The CST counselor will have prior experience in delivering behavioral interventions, particularly among African Americans. Prior to beginning this trial, the counselor will receive training in the pain CST intervention, including role-play sessions, with Dr. Somers. The counselor will also receive additional training in issues of cultural sensitivity regarding the CST program from Dr. Campbell. We will use four strategies to ensure the CST counselor consistently follows the appropriate treatment protocol: 1) the counselor will follow a detailed treatment outline and scripts, 2) supervision sessions (with Dr. Somers) will be conducted with the counselor, approximately weekly (with a likely reduction in frequency as the program progress), 3) audio-recorded CST sessions will be reviewed during supervision meetings, and the counselor's adherence to the protocol will be rated using a scale developed and utilized by Dr. Keefe and Colleagues. Satisfactory adherence will be defined as 90% or more of the maximum possible score on the adherence rating scale, and ratings will be derived from a randomly selected 15% (approximately) of all sessions, or more as deemed necessary. Dr. Campbell will also listen to recorded CST sessions, including approximately the first 10 sessions and 5% thereafter. Dr. Campbell will particularly focus her review on issues related to cultural relevance. Based on the project's sample size and projected rate of participant enrollment, the CST counselor will have sufficient time to conduct all sessions. However, in case back-up is needed to deliver some pain CST (due to counselor vacation, unexpected leave, etc.), we will also train another counselor who is currently on our VA study team (and who delivered the pilot study intervention), so we can avoid unexpected lapses in intervention delivery.

### **C.7.0 Patient-Centered Outcomes (PC-3, IR-4)**

**C.7.1 Overview (PC-2).** All study assessments will be conducted by trained research assistants, blinded to participants' randomization assignment. We will use scripts to ensure that measures are delivered in a consistent and valid manner. The CST counselor will not be involved in outcome assessments. Primary and secondary outcomes will be assessed at baseline (in-person), approximately 12-weeks (in-person) and 36 weeks (telephone). Participant characteristics will be assessed at baseline. Participants will be paid \$50 for completion of in-person assessments and \$25 for the 36-week telephone-based assessment. We have selected our pain-related outcomes on the basis of input from our Stakeholders (**RQ-6**) and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)<sup>87</sup>, which recommends measurement of four chronic pain domains: pain intensity (WOMAC pain subscale), physical functioning (WOMAC function scale), emotional functioning (Patient Health Questionnaire-8), and participant global impression of change. Other secondary patient-centered outcomes focus on self-efficacy, pain coping, quality

of life pain interference and pain medication use.

**C.7.2 Primary Outcome: WOMAC Pain Subscale.** We have chosen pain as the primary outcome because it is typically the chief complaint among patients with OA and affects other patient-centered outcomes (e.g., function, psychological health) (RQ-6). The WOMAC pain subscale is one of the most commonly used measures of pain among patients with lower extremity OA. It includes 5 items rated on a Likert scale of 0 (no symptoms) to 4 (extreme symptoms). The reliability and validity of the WOMAC total score and subscales have been confirmed<sup>88</sup>. Construct validity has been confirmed by a significant association with the Lequesne Algofunctional Index for Knees<sup>88</sup>. The WOMAC has been widely used in trials of behavioral interventions for patients with hip and knee OA, confirming its sensitivity to change in these types of interventions.

### C.7.3 Secondary Outcomes.

**WOMAC Total Score and Function Subscale.** In addition to the pain subscale, the WOMAC includes stiffness (2 items) and function (17 items) subscales. The WOMAC total score and function subscale are also common patient-centered outcomes for patients with lower extremity OA. We will assess the function subscale separately because of its importance as an outcome among patients with OA.

**Depressive Symptoms – Patient Health Questionnaire-8 (PHQ-8).** We have chosen to assess depressive symptoms because of their close association with pain<sup>89</sup>. These symptoms will be assessed using the PHQ-8, a reliable and valid measure<sup>90</sup>. The PHQ-8 is an eight-item survey that consists of items corresponding to depression criteria listed in the *Diagnostic and Statistics Manual Fourth Edition* (DSM-IV). Each of the eight questions is scored as 0 (not at all) to 3 (nearly every day), so that total scores range from 0 to 24.

**Patient Global Impression of Change.** We will use this scale to evaluate participants' perspectives on overall changes in their joint pain during the study period<sup>91</sup>. This measure asks participants to describe their change in pain on a 7-point rating scale with the following options: "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," and "very much worse." This scale has been widely used in clinical trials of chronic pain and is recommended by IMMPACT<sup>87</sup>.

**Coping Strategies Questionnaire (CSQ).** The CSQ is the most commonly used measure of coping among individuals with chronic pain, and its measurement properties have been confirmed in patients with a variety of pain-related conditions<sup>51,92</sup>. This scale includes 48 items that assess 6 cognitive domains (Catastrophizing, Diverting Attention, Ignoring Sensations, Coping Self-Statements, Reinterpreting Pain Sensations, Praying-Hoping) and 1 behavioral domain (Increasing Behavioral Activities). Each domain includes 6 items, and participants rate the frequency of their use of specific coping strategies on a 7-point Likert scale from 0 ("Never do that") to 6 ("Always do that"). The scale also includes two items that assess participants' perceived coping effectiveness, i.e. their subjective ability to control or decrease their pain, using a similar 7-point Likert scale.

**Arthritis Self-Efficacy Scale.** We will assess arthritis self-efficacy because of its close association with other OA-related outcomes (i.e., pain and function) and its patient-centeredness. The Arthritis Self-Efficacy Scale has shown acceptable construct validity (by its significant associations with pain, disability, and depression), internal reliability (alpha = 0.76-0.89), and test-retest reliability (Pearson r = 0.71-0.85). Higher scores on this scale have been significantly associated with improved health outcomes and protection against poor functional outcomes<sup>93,94</sup>. This scale includes 8 items asking respondents how certain they are that they can perform specific activities or tasks. Items are scored on a Likert Scale (1=very uncertain to 10=very certain).

**Health-Related Quality of Life (HRQoL).** We are including a measure of HRQoL based on feedback from our Patient Stakeholders, who stressed that OA affects many aspects of life and recommended that we broadly assess quality of life in this study (RQ-6). We will use the Short-Form-12 (SF-12), a validated measure that covers domains of general health, physical health, work and activity limitations, and emotional health<sup>95</sup>.

**PROMIS Pain Interference Instrument (Short Form)**<sup>96</sup>. The PROMIS Pain Interference (Short Form 6a) instrument measures the self-reported consequences of pain across aspects of life including social, cognitive, emotional, physical and recreational activities; this instrument refers to the past seven days. This validated scale has five response options, with scores ranging from one to five.

**Pain Medication Use.** Pain medications are a common treatment for patients with OA, and some patients seek to reduce their use; therefore we have included this as a secondary outcome. We will assess pain medication use using methods we have used successfully in previous studies. We will ask participants to bring

to their study visits (or bring to the telephone) all medications (prescription and non-prescription) they are currently taking for their arthritis symptoms. For each medication, the study team will record the medication name, medication class, frequency of taking the medication.

**Arthritis Self-Efficacy for Pain Communication Scale – Patient Version**<sup>97</sup>. This 7-item instrument assesses patient's level of confidence in communicating their pain to their partner and receiving understanding and a helpful response from their partner. Items are rated on a scale from 10 ("very uncertain") to 100 ("very certain").

**Starting the Conversation: Diet (STC)**<sup>98</sup>. The STC is an 8-item food frequency instrument that evaluates dietary assessment and intervention in a clinical setting. Response options for the survey are organized into 3 columns; one column indicating the most healthful dietary practices (scored 0), the 2<sup>nd</sup> column indicating less healthful practices (scored 1), and the 3<sup>rd</sup> column indicating the least healthful practices (scored 2).

**Brief Fear of Movement Scale**. The Brief Fear of Movement Scale is a six item scale for assessing fear of movement in OA. The scale specifically assesses activity avoidance due to pain-related fear of movement. All items are measured on a 4-point scale from "strongly agree" to "strongly disagree."

**Pain Catastrophizing Scale (PCS)**. The PCS is a widely used measure of catastrophic thinking related to pain<sup>99</sup>. This 13-item instrument asks participants to reflect on past painful experiences and to indicate the degree to which they experienced each of the thoughts or feelings when experiencing pain. The PCS includes 3 subscales – rumination, magnification, and helplessness.

**Pain Medication Use**. We will use a single-item measure that asks participants whether their overall pain medication use for OA has increased, decreased, or stayed about the same since the beginning of the study. Although this is a simple approach for measuring pain medication use, it is patient-centered, as it assesses patients' perceptions of how much they need to rely on medications to manage their OA-related pain.

**Time Missed From Work**. A single-item measure that asks participants about time missed from work will be used. This question asks participants how many work hours they have missed in the past month due to their osteoarthritis pain, other symptoms, and related healthcare visits.

**C.7.4 Participant Characteristics (RQ-4, IR-1)**. For Specific Aim#3, we will focus on evaluating potential differential effects of pain CST program, with particular interest in differences according to baseline pain catastrophizing (CSQ subscale), comorbidity (Self-Administered Comorbidity Questionnaire),<sup>100</sup> and self-reported duration of OA symptoms. We are interested in potential differences according to baseline pain catastrophizing because this domain of coping has a particularly strong, negative impact on pain-related outcomes. Therefore we are interested in understanding whether patients with higher catastrophizing scores at baseline, who may have the most room for benefit, experience greater improvement following the pain CST intervention. If pain catastrophizing predicts differential response, brief screening measures could be used in clinical settings to identify patients who may benefit most. We are interested in potential differences according to participants' comorbid health conditions, since these are highly common among individuals with OA and may be associated with implementation of coping strategies, as described in Section C above. We are interested in potential differences according on the duration of participants' OA symptoms so that we can understand whether patients may benefit differentially based on how long they have been dealing with symptoms. It is possible that patients could benefit most when early in the disease course, before unhelpful coping patterns may develop, but this is not known. Understanding this association will help to guide whether this type of program should be implemented systematically, early in the disease course.

We will also assess the following patient characteristics to describe the study sample: age, race/ethnicity, gender, marital status, household financial state, work status, education level, religiosity (Duke University Religion Index)<sup>101</sup>, body mass index (BMI; calculated from measured height and weight), physical activity (Yale Physical Activity Survey)<sup>102</sup>, joint involvement (i.e., report of all joints affected by arthritis), tobacco and alcohol use, and general self-rated health. Participants' baseline BMI and physical activity assessments will also be used by the CST counselor in delivering sessions 8 and 9; this will provide a foundation participants' current status regarding these two important lifestyle behaviors related to OA.

**C.7.5 Participant Feedback on CST Interventions**. As a part of 12-week follow-up assessments for the CST group, we will obtain participants' feedback on the intervention. This will include questions related to specific



content (e.g., perceived usefulness and suggestions related to each coping skill) and process (e.g. number and duration of sessions; See Appendix for full list of questions). This information will be used to by the study team, in conjunction with the Stakeholder Panel, to refine the program prior to dissemination of deliverables.

## **C.8.0 Analytic Methods**

### **C.8.1 Data Analyses**

**General.** Our statistical approach is guided by the PCORI Methods Report. The primary and secondary analyses will be conducted on an intent-to-treat basis; patients will be analyzed in the arm to which they were randomized, regardless of intervention adherence, using all data up to the 36 week follow-up or last available measurement prior to exclusion or dropout<sup>103</sup>. Additional supporting analyses focusing on alternative, more restrictive analytic cohorts (e.g., as treated) will be considered as exploratory analyses to provide additional information about the impact of magnitude of exposure to the intervention **(IR-5)**.

**Descriptive statistics.** Descriptive statistics, including graphical displays, will be used to summarize all study variables overall and by intervention arm. We will construct individual and mean trajectory plots of the longitudinal outcome variables to understand their general trends over the study period. In addition, we will explore the variability and correlation structure of outcome variables. All statistical analyses will be performed using the SAS (Cary, NC) software package / R ([www.r-project.org](http://www.r-project.org)).

**Missing Data (MD-2, MD-3, MD-5).** Because the main predictors of interest - intervention arm and patient characteristics - are collected at baseline, we do not anticipate much missing data in these variables. Our plans for preventing and dealing with missing data follow the guidelines set forth by the National Research Council's Panel on Handling Missing Data in Clinical Trials. Our goal is to achieve less than 20% attrition, which is very reasonable based on our prior and ongoing OA studies that include large proportions of African Americans<sup>19,62,64</sup>; we will use the same strategies of reminder calls, reminder letters and flexible scheduling to minimize attrition. There may be missing values in the outcome measures due to dropout, death, a missed interim assessment, or item non-response. Given a thorough understanding of the missing data mechanism, it is possible to use all of the available information in analysis, rather than using only subjects with completely observed information. Our main analysis technique for the primary outcomes, general linear mixed models via maximum likelihood estimation, implicitly accommodates missingness when missingness is due either to treatment, to prior outcome, or to other baseline covariates included in the model, defined as missing at random<sup>104</sup>. Therefore, inferences will be valid even if we have differential dropout by intervention arm. However as a first sensitivity analysis, we will construct a general, multivariate imputation model using all observed pain measurements, treatment arm, and any covariates predictive of missingness **(IR-5)**.<sup>105</sup> The primary model, specified below, will then be fit to the multiply imputed data and the estimates and standard errors will be combined using appropriate combining rules.<sup>106</sup> Multivariate imputation will be conducted via the SAS procedure PROC MI or the SAS macro IVEware (<http://www.isr.umich.edu/src/smp/ive/>). If the probability of dropout is related to the actual missing response (which is unobserved because it is missing) or to other unobserved quantities, the missing data due to dropout is considered missing not at random (MNAR) or nonignorable<sup>107</sup>. We propose as a second sensitivity analysis to explore MNAR methods, including pattern-mixture models and the toolkit of methods as presented in O'Kelly and Ratitch **(IR-5)**<sup>108</sup>.

**Primary Research Question: Among African Americans with OA, does a pain CST program result in improved pain and other patient-centered outcomes at 12-week and 36-week follow-up (Aim #2) (IR-3)**

We will use a linear mixed model (LMM) that will account for the correlation between a participant's repeated outcome measurements over time. Because of the small number of time points (3), we will apply an unstructured covariance matrix to take into account the within-patient correlation between repeated measures. The fixed-effect portion of the model will have the form:  $Y_{it} = \beta_0 + \beta_1 12week + \beta_2 36week + \beta_3 CST*12week + \beta_4 CST*36week$ , where  $Y_{it}$  is the WOMAC pain score for subject  $i$  at  $t=0, 12, 36$  weeks. We will estimate the parameters in the model using the SAS procedure MIXED (Cary, NC), and will test to see if there is a difference in mean WOMAC pain scores between the CST and WL groups at specified time points (i.e.,  $\beta_3=0$  and/or  $\beta_4=0$ ). Time is coded in this model to fit a constrained longitudinal data model (cLDA) in which baseline WOMAC pain is modeled as a dependent variable in conjunction with the constraint of a common baseline mean across the treatment arms<sup>109</sup>. In this way, the cLDA model is comparable to an ANCOVA model; the two



models are equivalent when there is no missing data. However, unlike an ANCOVA, subjects who are missing follow-up measurements are included in the model because baseline is part of the response vector. For improvement in precision, the model will also be adjusted for stratification variables of enrollment site and gender <sup>110</sup>. Similar procedures will be used for all continuous secondary outcomes. The secondary outcomes for pain medication use as defined in Section C.7.3 are either dichotomous or count type variables. We will fit a generalized logit model <sup>104</sup> using the SAS procedure NLMIXED for these outcomes.

**Secondary Research Question: Are individual patient characteristics (baseline pain catastrophizing score, duration of OA symptoms and comorbidity) associated with differential improvement in the pain CST program (Aim #3) (IR-3), HT-1-4, RQ-4).** Patients may vary in their response to the CST program; this variation is known as heterogeneity of treatment effects (HTE). We have selected three a priori patient characteristics (noted above) and will conduct a separate descriptive HTE for each, as defined in the PCORI Methods Report. We will construct individual and mean trajectory plots of the longitudinal outcome variables according to each characteristic and treatment arm to understand their general trends over the study period. Our general steps in this secondary analysis will be to add the patient characteristic main effect, as well as the interaction variables, to the linear mixed model defined above for primary analysis. We will examine the parameter estimates and 95% CI's for the 3-way interactions, treatment\*time\*patient characteristic, to determine whether there is evidence of HTE. New state-of-the art modeling methods have taken the exploration of HTE to the next level, making it possible to explore and identify multidimensional subgroups exhibiting heterogeneous treatment effects. We will explore whether the a priori defined patient characteristics define multidimensional subgroups that exhibit HTE. We will utilize two different analytic strategies for doing so: multivariable logistic regression (LR) <sup>111,112</sup> and recursive partitioning (RP) <sup>113,114</sup>. Our general steps in this secondary analysis will be: construction of outcome variables; identification of multidimensional subgroups via LR and RP; and, finally, examination of treatment effects within the multidimensional subgroups.

**Logistic Regression Methods:** We will construct a summary of each participant's repeated measures profile to characterize the participant's change over time. Empirical Bayes estimates from linear mixed-effects models with random intercepts and slopes will be used to generate individual-level estimates of mean improvement <sup>115</sup>. Multivariable logistic regression provides individual-level predicted probabilities of the binary outcome (i.e., improvement in pain) <sup>112</sup>. To generate these predictions, we will enter all a priori defined patient factors and interactions into a model to explain variation in study outcomes (beginning with the primary study outcome, WOMAC pain score) and apply backward selection with a type-I error rate of 0.01 to reach a final reduced model. We will then stratify the sample into quintiles on the basis of the predicted values. Then, we will estimate the constructed outcomes with a treatment main effect, the quintile indicators and an interaction term between treatment effect and each of the quintile indicators. The coefficients of these interaction terms will indicate whether improvements in outcomes differ between subgroups defined by quintiles.

**Recursive Partitioning Methods:** Our second approach will be the empirically driven iterative nonparametric process known as recursive partitioning. RP methods identify several subgroups that vary in their predictors and outcomes improvement, which have a clearer clinical intuition (e.g., participants with longer duration of OA symptoms, high comorbidity burden and high pain catastrophizing) compared to logistic regression <sup>113,114,116</sup>. We will conduct RP analysis using the R package "rpart" where all potential predictors will be included in the model statement. We will use the cross product prediction error to determine the optimal number of branches, and "prune" the tree back to the optimal number. The final product is a very clinically intuitive "tree" with "branches" <sup>116</sup>, with a predicted mean or proportion summarized at each terminal node. Treatment group can be included as part of the RP analysis to identify both predictors and moderators of treatment response; alternatively, treatment effect within each terminal node can be calculated to observe the clinical magnitude of effects across constructed subgroups.

**C.8.2. Additional Exploratory Analyses.** We may also conduct exploratory analyses of associations among other measures collected as part of this study. This may include associations among variables at baseline, potential roles of baseline variables as moderators or mediators of treatment effects, or association of baseline variables with intervention uptake and outcomes.

**C.8.3 Sample size.** The sample size estimate of  $n=124$  per arm is based on the primary research question. This involves testing the CST\*36week interaction in our model, as this will be the most conservative test due to higher attrition at the 36 week time point vs. 12 weeks. Sample size calculations use methods appropriate for ANCOVA type analyses<sup>117</sup>, which are equivalent in terms of efficiency to our linear model in randomized trials<sup>109</sup>. This method is based on performing a two-sample t-test sample size calculation for the between group difference, multiplied by a factor  $1-(\rho)^2$ , where  $\rho$  represents the Pearson correlation between baseline and follow-up time point outcome measures. This sample size is then adjusted to compensate for potential missing observations due to attrition. Based on previous data, we assume a correlation of 0.6 between baseline and follow-up WOMAC pain scores, and an SD of 3.9. With 80% power,  $\alpha=0.05$ ,  $SD=3.9$ ,  $\rho=0.60$ , and a conservative 20% attrition rate by 36 weeks<sup>62</sup>, we need to enroll 124 patients per group to detect a 1.3 point difference in mean WOMAC pain scores at 36 weeks between CST group and the WL control group. Based on a mean baseline WOMAC pain score of 9.2, this corresponds to approximately a 14% improvement or 0.33 (medium) effect size difference in WOMAC pain, which is a clinically relevant improvement<sup>20</sup>. Similarly, for the remaining secondary outcomes we will be powered to detect a 0.33 effect size difference for CST arm compared to the WL control group. We will have greater than 80% to detect a 1.3 point difference in pain scores between CST and WL at 12 weeks. We did not conduct a power analysis for the HTE analysis for Aim #3 because we are proposing a descriptive HTE and have followed the PCORI Methods Report on this issue.

**C.9.0 Data Management and Quality Control.** Study tracking data will be entered into a database we have developed at UNC as part of another clinical trial, which can be easily adapted for the proposed project. Screening and outcome measures will also be integrated into this database. Because we have used similar screening and outcome assessments in previous work, this will also facilitate programming of these tools. This database provides customized reports that have important functions for monitoring a clinical trial. These reports can provide immediate updates on the numbers of participants enrolled, excluded, withdrew, etc.. This will allow the study team to evaluate whether goals are being met and whether there are any differential rates of recruitment, drop-out, etc, according to patient demographic characteristics. These reports also facilitate easy checking of screening and outcomes data so the team can monitor for unexpected amounts of missing data (**MD-1**). The project coordinator will generate weekly reports, based on a CONSORT diagram, that describe all of these metrics related to study flow, as well as participant refusal, ineligibility and withdrawal reasons (**MD-4**). We will follow CONSORT guidelines for reporting study results (**IR-6**).

## D. PROJECT MILESTONES AND TIMELINE

Table 4 provides a timeline for all major activities and milestones. Aim 1 of the project involves engaging stakeholders (African American patients with OA, supportive partners, health care providers, clinic administrators, and public health representatives) in a process of evaluating and refining the pain CST program for cultural relevance and dissemination potential. We will complete this Aim in the first six months of the project. The draft materials for the CST program (including patient manual, intervention scripts, and audio instructions for progressive relaxation) are already prepared. These will be disseminated to the Stakeholder Panel and other team members prior to the first monthly meeting. At the beginning of the project, we will conduct an iterative process of incorporating stakeholder recommendations into the pain CST program (see Table 3 above). We will then engage approximately eight additional patients (and supportive partners when available) to provide additional feedback on the enhanced version of the pain CST program. We aim to have a final version of the CST program, informed by Stakeholders, by the end of Month 4. We will also disseminate other study-related materials to all stakeholders and study team members at the beginning of the project period. This will include the protocol and summary, outcome assessments, recruitment plan, timeline and milestone summary, plans and specific goals for dissemination and implementation activities.

**Table 4. Study Activities, Milestones and Timeline**

Activity / Milestone	Study Month
IRB Approval	Pre-funding period
Registration with Clinicaltrials.gov	Month 1
Complete Specific Aim #1 (Pilot Testing and Incorporation of Stakeholder Input on Pain CST	Month 4

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): ALLEN, KELLI DOMINICK

Program)	
Finalize Questionnaires and Protocol for Clinical Trial (Specific Aims #2 and #3)	Month 5
Submit Progress Report 1 and Engagement Update 1	Month 6
Complete All Start-Up Activities for Clinical Trial	Month 6
Submit Protocol Paper to Journal (Provide submitted & accepted versions to PCORI)	Month 7
Start of Recruitment (Target Total: N=248)	Month 7
Completion of 25% of Recruitment	Month 11
Completion of 50% of Recruitment	Month 15
Completion of 75% of Recruitment	Month 19
Completion of Recruitment	Month 23
Submit Progress Report 2 and Engagement Update 2	Month 12
Submit Progress Report 3 and Engagement Update 3	Month 18
Submit Progress Report 4 and Engagement Update 4	Month 24
Begin Submitting Abstracts and Manuscripts from Study Baseline Data (Provide submitted & accepted versions to PCORI)	Month 24
Complete 12-Week Follow-Up Assessments	Month 26
Begin Analyses of 12-Week Follow-Up Data	Month 27
Submit Progress Report 5 and Engagement Update 5	Month 30
Complete 36-Week Follow-Up Assessments	Month 32
Generate “Deliverables” Begin Dissemination of Results (See Dissemination and Implementation Section)	Month 33
Complete Final Study Analyses	Month 34
Complete Analytic Data Sets and Code Book	Month 34
Submit Main Study Outcome Paper (Provide submitted and accepted versions to PCORI)	Month 35
Submit Final Report	Month 36

Also during the first six months of the study, we will be engaged in other start-up activities related to Aims 2 and 3, the randomized clinical trial. These activities will include finalizing all databases (for screening, outcome assessment, and study tracking), training research assistants, and training the CST counselor. During the first six months the research assistants will also devote time to reviewing medical records from UNC and the Durham VAMC to identify potential study participants. This will provide a large pool of potentially eligible patients, to whom we will be ready to send recruitment letters, as soon as the clinical trial phase of the project begins.

The recruitment period for the clinical trial will be completed over a 17-month period (months 7-23). This will require enrollment of about 4 participants per week. Based on our experience with other OA-related clinical trials and the resources requested for this project, this is a very reasonable goal. Specifically, this will allow enough time for the research assistants to enroll the required number of new participants per week, while also completing 12-week and 36-week assessments. We will complete intervention delivery for participants in the CST group, as well as all 12-week follow-up assessments, by the end of month 26. 36-week follow-up assessments will be complete by month 32. All participants in the Waiting List Control group will complete their intervention (which begins after 36-week follow-up assessment) by month 36, the end of the project period.

We will routinely conduct data monitoring and data cleaning throughout the study period, so that analyses can be conducted efficiently and quickly. We will begin conducting analyses of baseline data as soon as those data are complete at month 23. Analyses of 12-week follow-up data will begin around month 27, and final analyses will be completed by Month 34. The last four months will also be our most intensive period regarding dissemination activities, described below.

## E. PATIENT POPULATION

### E.1.0 Patient Characteristics

This study will involve n=248 African Americans (based on self-reported race) with symptomatic hip or knee OA (RQ-3). The hip and knee are two of the most common joint sites for symptomatic OA and are main contributors to disability<sup>5</sup>. In addition, racial differences in pain and other outcomes have been reported

specifically among patients with OA in the hip and knee. Eligibility criteria were selected in order to include a representative sample of African American patients with OA, excluding only on the basis of criteria that would confound study outcomes or make it infeasible for patients to participate in the CST program. Participants must meet the following two criteria for at least one hip or knee:

- Diagnosis of Hip or Knee OA. This will be identified from UNC Health Care and Durham VAMC electronic medical records or based on participant self-report, with further evaluation at screening AND
- Current Joint Symptoms. We will use the Centers for Disease Control and Prevention's definition for persistent joint symptoms<sup>118</sup>. Participants must answer, "yes" to two questions: "In the past 12 months, have you had pain, aching, stiffness, or swelling in or around your (*joint(s) with OA*)?" and "Were these symptoms present on most days for the past month?"

Patients meeting any of the following criteria will be excluded: Diagnosis of gout (in knee or hip), rheumatoid arthritis, fibromyalgia, other systemic rheumatic disease; Dementia or other memory loss condition; Active diagnosis of psychosis, serious personality disorder, or current uncontrolled substance abuse; Total hip / knee replacement surgery, other knee / hip surgery, ACL tear, or other significant knee/hip injury in the past 6 months; Scheduled for or on a waiting list for joint replacement surgery; Severely impaired hearing or speech (patients must be able to participate in telephone sessions); Unable to speak English; Participating in another OA intervention study or coping skills training study; Unwilling to be randomized either study arm; Lower extremity paralysis; Other health problem that would prohibit participation in the study (at the discretion of the Principal Investigator).

We plan to enroll equal numbers of participants (n=124) from UNC Health Care and the Durham VAMC. We recently completed a data pull of patients with diagnoses of OA within the UNC Health Care System. This resulted in over 10,000 patients; based on this overall number we are confident there will be an ample number of African American patients who are eligible to participate (**PC-2**). At the Durham VAMC, we base our estimate of potentially eligible patients on a data pull of African American patients with ICD-9 codes for hip and / or knee OA (which we have found to be more consistently used than in the Duke healthcare system) and no ICD-9 codes for study exclusion criteria. During FY 2011, there were approximately 1,970 African American patients at the Durham VAMC who met these criteria, and the patient population has increased in volume since then. Applying the estimated 29% enrollment rate based on our prior research<sup>62</sup>, this would result in n=570 patients at the Durham VAMC, which also far exceeds our enrollment goal of n=124 (**PC-2**).

Participants will be withdrawn from the study if they develop any new health problems or other events that would either a) make participation in the study intervention or measures unsafe or b) confound study outcomes. These largely mirror study exclusion criteria. In particular, participants will be asked if they have had a total joint replacement (knee or hip) surgery, other significant knee or hip surgery, or ACL tear prior to their 12-week and 36-week assessments.

### **E.2.0 Recruitment Process (PC-2)**

We will include three methods of recruitment, which we have successfully utilized in prior studies. First, we will use a variety of methods to advertise the study to potential participants. These may include: posting flyers and brochures in UNC clinics; advertisements on a UNC website and other websites appropriate for reaching our target patient group; advertisements in newsletters, magazines and other appropriate print media; email blasts to UNC employees; advertisement on the UNC closed circuit television. Flyers and brochures may also be distributed by health care providers. Second, providers will be able to refer patients to the study team directly, with patients' permission. Third, we will use UNC and Durham VAMC medical records to identify patients with diagnoses of hip or knee OA and no exclusionary diagnoses, and we will mail and/or email invitation letters to these patients. (We will initially identify African American patients based on documented race in the medical record, but we will ultimately base enrollment on self-reported race assessed during telephone screening.) For self-referred or provider-referred patients we will also check for exclusionary diagnoses in UNC or Durham VAMC medical records. All potential participants will undergo a brief telephone screening questionnaire to check for eligibility criteria. If patients meet screening criteria and are interested in participating, they will be asked to meet a study team member at their clinic to complete consent and baseline assessments.



We will implement an enhanced informed consent process that includes education about the research process and participant bill of rights. Participants will be mailed the “You’ve Got the Power!” booklet prior to their enrollment visit; this was developed and is distributed by the National Medical Association as part of Project IMPACT – Increase Minority Participation and Awareness of Clinical Trials. In addition, we will show all potential participants the nine-minute “What You Should Know About Clinical Trials” video produced by this same organization, at the beginning at the baseline visit. This video includes basic information about clinical trials and perspectives from African Americans who have participated. All study personnel will be trained in issues related to cultural relevance, including potential distrust of medical institutions and research among African Americans<sup>119</sup>.

During the baseline assessment, UNC participants will be asked for the name of their main UNC physician so that we may send their doctor a message (through EPIC or by mail) making them aware of their patients’ participation in the study.

Following baseline assessments, participants will be given their randomization assignment via telephone by the project coordinator (since the research assistants conducting baseline study assessments will be blinded to participants’ study group). Randomization will be based on a computer generated sequence maintained by the project statistician. We will mail participants in the CST group their patient manual and relaxation audio-recording prior to the first CST program telephone session. The audio recording may also be sent via email or posted on a website for participants to access. Participants randomized to the WL group will be informed they will begin the CST program after their follow-up assessments are complete.

## F. RESEARCH TEAM AND ENVIRONMENT

As described in the preliminary studies section above, our study team has extensive experience in areas of high relevance to the proposed project, including: development and testing of pain CST programs (Drs. Keefe, Somers, and Campbell), clinical trials among patients with OA, including large proportions of African Americans (Drs. Allen, Oddone, Keefe, Somers, and Campbell), cultural enhancements to pain CST interventions and minority health research (Dr. Campbell), and health services interventions (Drs. Allen and Oddone). Drs. Allen and Campbell also have experience with Stakeholder Panels as investigators on other PCORI-funded research. The study Stakeholder Panel, described below, is also highly qualified to ensure relevance of the study and facilitate dissemination in multiple spheres. All participating institutions have robust research environments that include support for study-related activities including: interview / enrollment space, computer / IT support and infrastructure, budget and logistical support, regulatory support, and resources for investigators’ professional development.

As noted above, the study will take place in two different primary care settings – UNC Health Care and the Durham VAMC - to enhance generalizability and provide an opportunity to evaluate feasibility of implementation in these differing environments (**PC-2**). UNC Healthcare is a large not-for-profit integrated health care system associated with the UNC School of Medicine; it includes many community-based clinics across central NC and serves a diverse patient population. Over 780,000 are treated at UNC ambulatory care clinics annually. At UNC we will focus enrollment on clinics that serve a high proportion of African American patients, including the Ambulatory Care Center. The VA healthcare system is the largest integrated in the U.S. and serves a patient group that has poorer physical and psychological health and lower socioeconomic status than the general population. The VA also serves a large proportion of men, providing an important opportunity to evaluate this pain CST program in a study sample that includes a larger proportion of men than are typically involved in OA studies. The Durham VAMC serves over 47,000 veterans, about 68% of whom are age 55 or older and therefore in the prime age category for the development of OA. About 1/3 of patients are African American. At the Durham VAMC we will include patients who are currently enrolled in Ambulatory Care.

Recruitment and outcome assessment activities will take place at both study sites, for patient convenience. The database with study outcome, tracking, and intervention-related data will be housed at UNC; for patients enrolled from the Durham VAMC, we will request permission to house data at UNC as part of the consent process. All pre-consent data for the Durham VAMC will be housed in a database that resides at the VA. Dr.



Somers at Duke will oversee the CST counselor. This will require that she listen to audio tapes of CST phone calls; these will remain on a UNC server.

## G. ENGAGEMENT PLAN

Key Stakeholders for this project are African American patients with OA, their supportive partners, health care providers, and public health and health service leaders (**PC-1**). The Appendix includes a list of Stakeholder Panel Members. We describe here our engagement of these Stakeholders to date and plans for continued engagement throughout the study period (**PC-1**).

### G.1.0 Planning the Study

**Pilot Studies of Pain CST Intervention.** As described above, our team has completed a pilot study of a pain CST intervention among African American Veterans with OA. This included both focus groups and individual interviews, where patients provided us with feedback on the program. Participants expressed a high degree of satisfaction with and appreciation for the program, which corroborated the improvements in pain-related outcomes described above. **This very positive response by patients in the pilot study was the primary motivator for the study team to proceed with a larger study to build the evidence base for this program among African Americans with OA.** The following are example comments from pilot study participants:

*“The program has given me so many tools in order to actually deal with the arthritis pain.... It’s a lot of tools that they have given me, you know, the pleasant thoughts and the mini relaxation and then the relaxation that you know you do the whole full body one. There’s so many things that you can do that I have done and I’m beginning to do to deal with the pain, so the program has been a tremendous help.”*

*“You know it makes my day, because if I get into a situation where something difficult because I’m having the pain then I can apply those skills.”*

*“Well, before the study...I was kind of locked in to the idea that eventually I was going to have to have the knee replacement. But once the study came in to play, I realized that I can cope with this and up until there really was an alternative.” “And I think that the program probably, I’m sixty-two years old, would have probably put me at a place that I may never get the operation now, never.”*

*“Before the program I really didn’t have the right tools in order to get rid of the pain. Now, more times than not, I actually do have tools in order to be able to make the pain decrease without having to use medication and it actually works out for a lot more than just the pain. It actually helps with stress, and I would think that in certain situations the stress helps to actually cause a lot of the pain.”*

In qualitative interviews following the pilot intervention, participants noted that one unexpected result of the program was that they were able to decrease their reliance on pain medications. Based on this we have added assessments of pain medication use to this study. One example comment was:

*“The program has helped tremendously because it helps to be able to cope with pain, it helps cope with a lot of other stuff and for some reason, for me, it allowed me to get to a point where I didn’t have to take quite as much meds to control the pain because it allowed me to use my mind to do what I needed to get done as opposed to medication, which was a crutch for me because I hate taking medicine. I’d much rather be able to do it with my mind than to do it with meds.”*

Pilot study participants also appreciated the flexibility and convenience of the telephone-based delivery. They liked the “*opportunity to be able relax in the comfort of my house,*” and “*not having to take off work to go driving.*” Therefore the telephone-based delivery has been retained for this larger study.

**Additional Stakeholder Engagement in Planning the Study.** We have been meeting with Patient Stakeholders from our enrollment sites, as well as supportive partners (when available), who have reviewed aspects of the project including the research questions, outcomes, recruitment plans, intervention content, and dissemination plans. Examples of specific ways in which Patient Stakeholders influenced the study plan include the addition of a Communication module to the pain CST program (described above) and addition of a global health-related quality of life measure as a patient-centered outcome. We have also obtained input on the study design and methods from clinical and public health stakeholders. These individuals will be particularly instrumental in downstream implementation processes and have already helped the study team to focus on these issues and potential barriers.

### G.2.0 Conducting the Study.

Throughout the study, we will hold monthly meetings (or email updates as appropriate) with the Stakeholder Panel. Some stakeholders may participate via telephone because of their geographic location. These meetings will include updates on study progress, requests for input from the Panel on any current study issues or questions, and an opportunity for general discussion and questions from the Panel. We have developed progress report templates in our prior and ongoing clinical trials, which will be used to provide study update and monitoring information to the Panel. These include summaries of key events and activities, a flow chart (e.g., CONSORT diagram) describing study enrollment, and description of participant characteristics that will allow Panel members to evaluate whether we are adequately enrolling a diverse sample (e.g., gender, age, religiosity, education, income). If stakeholders cannot make a meeting, Dr. Allen will communicate with them via email and / or phone to provide an update and get their input on any issues discussed.

The start-up period will be a particularly important and active time for the Stakeholder Panel, as we will be asking for their input on various study materials and logistics prior to enrolling patients. We will use processes for this engagement that we have found to be successful in our current PCORI-funded project. Specifically, we will disseminate materials for review prior to a monthly meeting / call. Panel members will be asked to review the materials and provide feedback to Dr. Allen and the study team before and / or during the meeting. We have found that disseminating these materials ahead of time facilitates meaningful and fruitful group discussion during the meeting. Examples of materials / processes we will ask the Stakeholder Panel to review during the start-up period are: Final measurement battery, CST program scripts, CST program handouts, Recruitment materials, and Recruitment processes.

We will also meet individually with our Patient Stakeholders during the start-up period, so that we may spend focused time in obtaining their input on recruitment materials (introductory letter, telephone screening script) and consent language. Dr. Allen will have individual conversations with all Stakeholder Panel members throughout the study, to discuss whether they perceive they are meaningfully involved in the project and that their contributions are valued and incorporated. We plan for these discussions to occur after 6-months, 12-months, and annually thereafter. However, if discussions indicate a need for more frequent check-ins or other actions, we will modify this plan accordingly.

### G.3.0 Disseminating the Study Results

A detailed description of our dissemination plans is described in the Dissemination and Implementation Potential section. Here we provide a summary of Stakeholder Panel involvement in these activities:

- The study team will create Patient Testimonial Videos; these will be brief interviews with patients who participated in the CST program, describing their experiences and perceived benefits. These will be used in multiple dissemination activities, including posting on websites and use in live presentations.
- Patient Stakeholders will provide recommendations for venues for presenting study results in the community (e.g., senior centers, other organizations in which they are active – particularly those that serve a high proportion of older African Americans, and local media or print resources).
- Patient Stakeholders will review dissemination materials, particularly those geared toward lay distribution.
- Public Health Leaders (e.g., Arthritis Foundation, Centers for Disease Control and Prevention) will facilitate broad dissemination of study findings and deliverables through their organizations' newsletters, other publications, and websites.
- Clinician Stakeholder Panel Members will help to organize presentation of study results to other health care providers (e.g., during Grand Rounds and Clinic / Service Team meetings).
- All Stakeholder Panel members will be invited to co-author manuscripts.

### G.4.0 PCORI Engagement Principles

#### **Reciprocal Relationships**

Stakeholder Panel members bring valued perspective to the study team and have expertise and experience in areas that differ from other team members. **The over-arching principle of our study team is that all members' contributions are of equal value.** When the team is considering questions related to the study, all members will have opportunity to voice their opinions. Since participation on a research team may will be new for some Patient Stakeholders, we will make special effort to ensure these individuals are able to

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share their opinion in a manner that is comfortable to them. As noted above, Dr. Allen will have individual in-person meetings with Patient Stakeholders, providing them with another opportunity to share opinions they may be less comfortable expressing in a larger study team meeting. We recognize that there may be situations when team members have differing opinions regarding study-related decisions. If these situations arise, Dr. Allen as Principal Investigator will be responsible for resolution, with a commitment to equal value among team member perspectives, an aim of identifying a solution that is acceptable to all team members, and preservation of both patient-centeredness and scientific integrity. At the beginning of the study period, Dr. Allen will circulate a document to study team members, describing study team roles, expectation of equal value among study team member perspectives, and a framework for resolving disparate opinions if they occur. All team members will be asked to sign this document indicating a commitment to these principles.

### **Co-Learning**

At the beginning of the study period, we will provide basic research training to Stakeholder Panel members, particularly those who have not previously been part of a study team. We plan to use three primary resources for this training, which will be provided in person by Dr. Allen. The first is a module developed by UNC Chapel Hill for training patient partners, which focuses on guiding principles, privacy and participant rights. The second is another module developed locally (Duke University Medical Center and Durham VA Medical Center) that provides an overview of clinical trial research methods. Both of these modules consist of sets of power point slides, in easy-to-read terms, which will be given to Stakeholder Panel members as handouts following in-person training. The third resource is a lengthier document, “Understanding Clinical Trial Design: A Tutorial for Research Advocates,” developed by the Research Advocacy Network. Because sections of this document are above “lay language,” we will summarize key points from this document into a slide set that will complement the other two resources described above. We also recognize that best practices and resources for Stakeholder training are emerging, and we will incorporate new materials into this training as they become available.

We will also provide training to all study team members regarding meaningful Stakeholder Engagement. All members will become familiar with PCORI’s Engagement Rubric, to provide a basic understanding of expectations and roles of Stakeholders. Study team members will also watch the PCORI webinar on “Promising Practices of Meaningful Engagement in the Conduct of Research” and the archived Institute of Medicine video, “Partnering with Patients to Drive Shared Decisions, Better Value and Care Improvement.” We realize that best practices for Stakeholder Engagement are emerging, and we will also utilize any other locally and nationally available training resources that become available by the study period.

### **Partnership**

Stakeholder Panel members will be paid \$100 for participation in each monthly meeting. This will help to compensate Panel members for their time and effort. (Employees of the Centers for Disease Control and Prevention and the Department of Veterans Affairs cannot be compensated financially for these activities, but these Stakeholders have confirmed they are able to participate based on their normal work responsibilities, per Letters of Support). Panel members have agreed that monthly meetings are a reasonable time commitment, as noted in their Letters of Support. In the process of planning monthly meetings, we will poll Panel members for their times of availability. As we have done in the past, we will also meet individually, in person, with Patient Stakeholders to foster those relationships and allow concentrated time to receive their feedback on aspects of the study; we will meet at locations convenient to and selected by Patient Stakeholders.

### **Trust, Transparency, and Honesty**

All study team members will be asked to sign document committing themselves to equal value among study team member perspectives and a framework for resolving differing opinions. This document will also describe roles of the study team members and general principles of mutual respect. We will foster transparency through regular (monthly) reporting of study progress and opportunities for all team members to ask questions and provide input on study processes. At the completion of the study, we will prepare an overview of findings; this will be mailed to all study participants (after review by Patient Stakeholders).

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